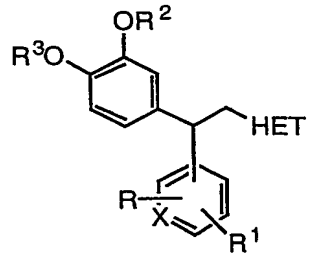
WHAT IS CLAIMED IS:

1. A method of treatment of rheumatoid arthritis by administering, to one in need of such treatment, an effective amount of a phosphodiesterase-4 inhibiting compound.

2. A method of treatment of rheumatoid arthritis by administering, to one in need of such treatment, an effective amount of a compound represented by Formula (I):



(I)

or a pharmaceutically acceptable salt thereof wherein:

R is hydrogen, C_{1-6}alkyl, halogen or CF_3;

R^1 is $-(CH_2)_m$-CO-N(R^4)-S(O)$_2$-R^5, $-(CH_2)_m$-CO-N(R^4)-S(O)$_2$-NR^6R^7, $-(CH_2)_m$-S(O)$_2$-N(R^4)-CO-R^4, $-(CH_2)_m$-S(O)$_2$-N(R^4)-CO-NR^6R^7, or -C(OH)(C_{1-6}haloalkyl)$_2$, wherein m is 0, 1 or 2,

R^2 and R^3 are each independently C_{1-7}alkyl, substituted C1-7 alkyl, wherein the substituent is F, Cl, Br or I, 2-phenethyl or 2-indanyl, optionally mono or di-substituted, wherein the substituents on the benzene ring are each independently halogen, -C_{1-6}alkoxy, -C_{1-6}alkylthio, -CN, -CF_3, -C_{1-6}alkyl, -N_3, or -CO_2H,

R^4 is hydrogen, -C_{1-6}alkyl, phenyl, benzyl or 2-phenethyl, optionally mono or di-substituted, wherein the substituents on the benzene ring are independently halo, -C_{1-6}alkoxy, -C_{1-6}alkylthio, -CN, -CF_3, -C_{1-6}alkyl, -N_3, or -CO_2H,

R^5, R^8 and R^{11} are each independently -CF_3, -C_{1-6}alkyl, phenyl, benzyl or 2-phenethyl, optionally mono or di-substituted, wherein the substituents on the benzene ring are independently halogen, -C_{1-6}alkoxy, -C_{1-6}alkylthio, -CN, -CF_3, -C_{1-6}alkyl, N_3, or -CO_2H,

R^6, R^7, R^9 and R^{10} are each independently hydrogen, or -C_{1-6}alkyl, or

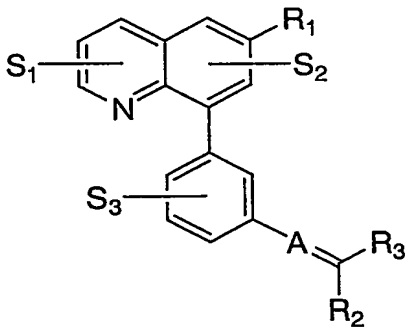
R^6 and R^7 may be joined to form a saturated 5, 6 or 7 membered heterocycle, said heterocycle containing a heteroatom which is nitrogen and optionally containing an

additional hetero atom which is an O or an S atom or NR^4 , and optionally containing a carbonyl group;

HET is pyridyl or imidazolyl, optionally mono-, or disubstituted, wherein the substituents are independently halogen, -C_{1-6}alkyl, -C_{1-6}alkoxy, -C_{1-6}alkylthio, benzyl, 2-phenethyl, -$NHCOR^8$, -NR^9R^{10}, -$NHS(O)_2R^{11}$, OH, -CN, or -CF_3, or the N-oxides thereof; and

X is N, N→O, or CH.

3. A method of treatment of rheumatoid arthritis by administering to one in need of such treatment an effective amount of a compound represented by Formula (II):



(II)

or a pharmaceutically acceptable salt thereof, wherein

S_1, S_2, and S_3 are independently H, -OH, halogen, -C_1-C_6alkyl, -NO_2, -CN, or -C_1-C_6alkoxy, wherein the alkyl and alkoxy groups are optionally substituted with 1-5 substituents; wherein each substituent is independently a halogen or OH;

R_1 is a H, OH, halogen, or -C_1-C_6alkyl, -cycloC_3-C_6alkyl, -C_1-C_6alkenyl, -C_1-C_6alkoxy, aryl, heteroaryl, -CN, -heterocycloC_3-C_6alkyl, -amino, -C_1-C_6alkylamino, -(C_1-C_6alkyl)(C_1-C_6alkyl)amino, -C_1-C_6alkyl(oxy)C_1-C_6alkyl, -C(O)NH(aryl), -C(O)NH(heteroaryl), -SO_nNH(aryl), -SO_nNH(heteroaryl), -SO_nNH(C_1-C_6alkyl), -C(O)N(C_0-C_6alkyl)(C_0-C_6alkyl), -NH-SO_n-(C_1-C_6alkyl), -SO_n-(C_1-C_6alkyl), -(C_1-C_6alkyl)-O-C(CN)-dialkylamino, or -(C_1-C_6alkyl)-SO_n-(C_1-C_6alkyl) group, wherein any of the groups is optionally substituted with 1-5 substituents; wherein each substituent is independently a halogen, -OH, -CN, -C_1-C_6alkyl, -cycloC_3-C_6alkyl, -C(O)(heterocycloC_3-C_6alkyl), -C(O)-O-(C_0-C_6alkyl), -C(O)-aryloxy, -C_1-C_6alkoxy, -(C_0-C_6alkyl)(C_0-C_6alkyl)amino, cycloalkyloxy, acyl, acyloxy, -cycloC_3-C_6alkyl, heterocycloC_3-C_6alkyl, aryl, heteroaryl, carbamoyl, or -SO_n-(C_1-C_6alkyl);

A is CH, C-ester, or C-R4;

R2 and R3 independently is an aryl, heteroaryl, H, halogen, –CN, -C1-C6alkyl, heterocycloC3-6alkyl, -C1-C6alkoxy, carbamoyl, -C(O)OH, -(C1-C6alkyl)-SOn-(C1-C6alkyl), -C(O)N(C0-C6alkyl)(C0-C6alkyl), or -C1-C6alkylacylamino group, wherein any of the groups is optionally substituted with 1-5 substituents, wherein each substituent is independently an aryl, heteroaryl, halogen, -NO2, -C(O)OH, -CN, -C1-C6alkyl, -SOn-(C1-C6alkyl), -SOn-(aryl), aryloxy, -heteroaryloxy, C1-C6alkoxy, N-oxide, -C(O)-heterocycloC3-C6alkyl, -NH-cycloC3-C6alkyl, amino, -OH, or -(C0-C6alkyl)(C0-C6alkyl)amino, -C(O)-N(C0-C6alkyl)(C0-C6alkyl) substituent group, wherein each substituent group independently is optionally substituted with -OH, C1-C6alkoxy, -C1-C6alkyl, -cycloC3-C6alkyl, aryloxy, -C(O)OH, -C(O)O(C1-C6alkyl), halogen, -NO2, -CN, -SOn-(C1-C6alkyl), or -C(O)-N(C0-C6alkyl)(C0-C6alkyl);

one of R2 and R3 must be an aryl or heteroaryl, optionally substituted;

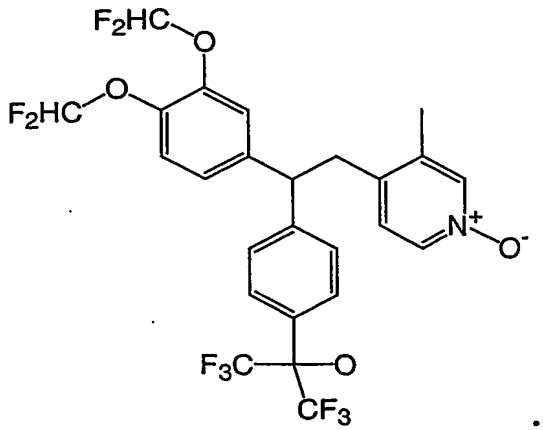
when R2 and R3 are both an aryl or heteroaryl, then R2 and R3 may be optionally connected by a thio, oxy, or (C1-C4alkyl) bridge to form a fused three ring system;

R4 is an aryl, -C1-C6alkyl, heteroaryl, –CN, carbamoyl, -(C1-C6alkyl)-SOn-(C1-C6alkyl), -C(O)N(C0-C6alkyl)(C0-C6alkyl), or -C1-C6alkylacylamino group, wherein any of the groups is optionally substituted with 1-5 substituents, wherein each substituent is independently a -CN, halogen, -C(O)(C0-C6alkyl), -C(O)O(C0-C6alkyl), -C1-C6alkyl, -SOn-(C1-C6alkyl), -OH, C1-C6alkoxy, or -(C0-C6alkyl)(C0-C6alkyl)amino, group;

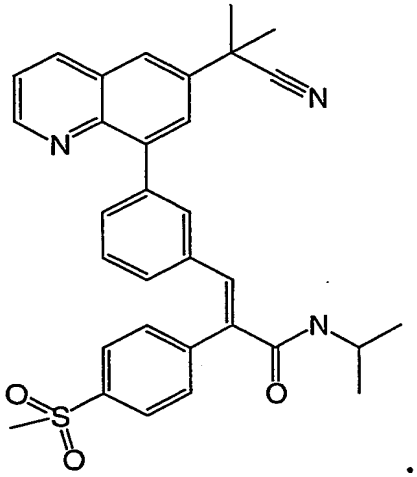
n is independently 0, 1, or 2; and

R2 or R3 may optionally be joined to R4 by a bond to form a ring.

4. The method of claim 2, wherein said compound is represented by

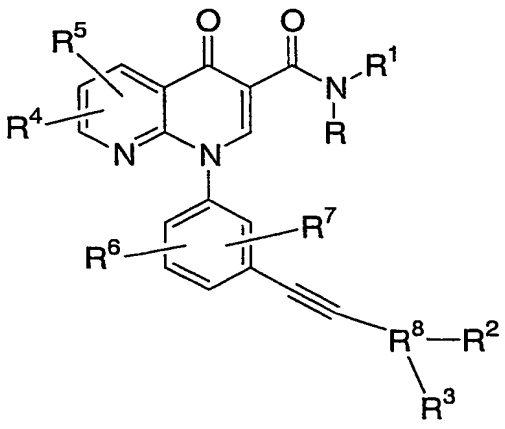


5. The method of claim 3, wherein said compound is represented by



6. A method of treatment of rheumatoid arthritis by administering to one in need of such treatment an effective amount of N-(3,5-dichloropyrid-4-yl)-3-cyclopropylmethoxy-4-difluoromethoxybenzamide.

7. A method of treatment of rheumatoid arthritis by administering, to one in need of such treatment, an effective amount of a compound represented by Formula (III):



(III)

or a pharmaceutically acceptable salt thereof, wherein

R is H, $-C_{1-6}$alkyl or $-C_{3-6}$cycloalkyl;

R^1 is H, or a $-C_{1-6}$alkyl, $-C_{3-6}$cycloalkyl, $-C_{1-6}$alkoxy, $-C_{2-6}$alkenyl, $-C_{3-6}$alkynyl, $-C(O)-C_{1-6}$alkyl, -C(O)-aryl, $-(C_{0-6}alkyl)-SO_n-(C_{1-6}alkyl)$, $-(C_{0-6}alkyl)-SO_n-$(aryl), phenyl, heteroaryl, or heterocycloC_{3-7}alkyl group, wherein any of the groups is optionally substituted with 1-3 independent $-C_{1-6}$alkyl, $-C_{1-6}$alkoxy, OH, $-N(C_{0-6}alkyl)(C_{0-6}alkyl)$, $-(C_{0-6}alkyl)-SO_n-(C_{1-6}alkyl)$, nitro, CN, =N-O-$C_{1-6}$alkyl, -O-N=$C_{1-6}$alkyl, or halogen substituents;

R^2 is absent, H, halogen, $-C_{1-6}$alkyl, $-C_{3-6}$cycloalkyl, $-C_{1-6}alkyl(C_{3-6}cycloalkyl)(C_{3-6}cycloalkyl)$, $-C_{1-6}$alkoxy, phenyl, heteroaryl, heterocycloC_{3-7}alkyl, nitro, CN, =N-O-C_{1-6}alkyl, -O-N=C_{1-6}alkyl, $-N(C_{0-6}alkyl)(C_{0-6}alkyl)$, $-NHSO_n-(C_{1-6}alkyl)$, $-NHC(O)-C_{1-6}$alkyl, -NHC(O)-aryl, $-C(O)-C_{1-6}$alkyl, $-C(O)-O-C_{1-6}$alkyl, $-C_{1-6}alkyl(=N-OH)$, $-C(N=NOH)C_{1-6}$alkyl, $-C_{0-6}alkyl(oxy)C_{1-6}$alkyl-phenyl, $-SO_nNH(C_{0-6}alkyl)$, or $-(C_{0-6}alkyl)-SO_n-(C_{1-6}alkyl)$, wherein the phenyl, heteroaryl or heterocycloC_{3-7}alkyl is optionally substituted with halogen, $-C_{1-6}$alkyl, $-C_{1-6}$alkoxy, hydroxy, $-N(C_{0-6}alkyl)(C_{0-6}alkyl)$, or $-C(O)-O-C_{1-6}$alkyl, and any alkyl is optionally substituted with 1-6 independent halogen or –OH substituents;

n is 0, 1, or 2;

R^3 is absent, H, OH, $-N(C_{0-6}alkyl)(C_{0-6}alkyl)$, halogen or C_{1-6}alkyl, wherein any alkyl is optionally substituted with 1-6 independent halogen, OH, or $-N(C_{0-6}alkyl)(C_{0-6}$alkyl) substituents;

R^4, R^5, R^6, and R^7 each independently is H, halogen, $-C_{1-6}$alkyl, $-C_{1-6}$alkoxy, $-SO_n-(C_{1-6}alkyl)$, nitro, CN, or $-N(C_{0-6}alkyl)(C_{0-6}alkyl)$, and any alkyl is optionally substituted with 1-6 independent halogen or –OH substituents; and

R^8 is phenyl, pyridyl, pyrimidyl, indolyl, quinolinyl, thienyl, pyridonyl, oxazolyl, oxadiazolyl, thiazolyl, thiadiazolyl, or imidazolyl; or oxides thereof when R^8 is a heteroaryl; or H, $-C_{1-6}$alkyl, or $-C_{3-6}$cycloalkyl, and any alkyl is optionally substituted with 1-6 independent halogen, $-N(C_{0-6}alkyl)(C_{0-6}alkyl)$, $-N(C_{3-7}cycloalkyl)(C_{0-6}alkyl)$, $-N(C_{3-7}cycloalkyl)(C_{3-7}$cycloalkyl), *N*-heterocycloC_{4-7}alkyl, $-SO_n-(C_{1-6}alkyl)$, $-SO_n-$(aryl), or –OH substituents.